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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,586	09/11/2001	Melissa M. Cunningham	GP116-03.UT	7245

21365 7590 10/31/2005

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/954,586	CUNNINGHAM ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *164-264* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *164-177,180-218 and 225-259* is/are rejected.

7)☒ Claim(s) *178,179,219-224 and 260-264* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed August 9, 2005. Currently, claims 164-264 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Priority

4. This application claims priority to U.S. Provisional Application No. 60/232,028, filed September 12, 2000.

Drawings

5. The drawings are acceptable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 164-177, 180-218, 225-259 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (J. of Infectious Disease, Vol. 177, pages 1443-1446, 1998) in view of Williams et al. (US Pat. 6,146,855, November 14, 2000) and Xiao et al. (Applied and Environmental Microbiology, Vol. 65, No. 8, pages 3386-3391, August 1999) in view of Hogan (US Pat. 5,595,874, January 1997).

The broad product claims have also been rejected in this 103 rejection. The unexpected results of the primer pair of SEQ ID NO: 46 and 59 have been considered, however, many of the claims are not limited to the primer pair consisting of SEQ ID NO: 46 and 59 which have the unexpected properties over SEQ ID NO: 45 and 59.

Zhu et al. (herein referred to as Zhu) teaches a method of detecting *Cryptosporidium* using genus specific primers from the 18S rRNA. The target DNA for PCR was the small subunit rRNA gene (srDNA).

Zhu does not specifically teach using SEQ ID NO: 46, 59 as a target sequence for the probes and primers.

However, Williams et al. (herein referred to as Williams) provides an alignment for the relatedness in Figure 3A between *C. parvum, C. muris, C. baileyi.* The

positions of specific *C. parvum* 18S rRNA probes in respect of the whole 18S rRNA sequence is illustrated. SEQ ID NO: 46, 59 are embedded within the sequences.

Moreover, Xiao et al. (herein referred to as Xiao) teaches a comparison study of seven Cryptosporidium various isolates from various hosts. The species include *C. parvum, C. wrairi, C. muris* and *C. baileyi*. Xiao teaches that the nucleotide sequences of the parasites were deposited in GenBank under various accession numbers. Xiao teaches aligning the sequences and identifying differences among the isolates.

Moreover, Hogan teaches a method which compares one or more sequence rRNA variable regions from a target organism to one or more rRNA variable region sequences from closely related species that can be utilized to distinguish between such organisms. Hogan teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various

> assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (col. 10, lines 13-15)(limitations of Claims 4-6). Oligonucleotides complementary to sequences adjacent to the probe regions were synthesized and used in the hybridization mix according to Hogan et al., U.S. Pat. No. 5,030,557; filed Nov. 24, 1987, entitled "Means and Method for Enhancing Nucleic Acid Hybridization (the "helper " patent application). Hogan teaches that oligonucleotide probes may be labeled by any of several well known methods such as radioisotopes, non-radioactive reporting groups, non-isotopic materials such as fluorescent molecules (col. 10, lines 45-60). Hogan teaches that probes may be labeled using a variety of labels, as described within, and may be incorporated into diagnostic kits(limitations of Claims 74, 88, 135-155).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the genus specific PCR primers taught by Zhu using the alignment provided by Williams and Xiao and the specific guidance provided by Hogan to obtain the invention as a whole. The probes of Williams are located in the same region as SEQ ID NO: 5, for example. Given the teachings in the art directed to modifying probes and primers to obtain functional equivalents, the ordinary artisan would have been motivated to have selected any other probe or primer

which would function to detect and discriminate C. parvum from other Cryptosporidium species.

Since the claimed primers simply represent functional equivalents of the probes and primers of Zhu, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. The specific probes, absent any unexpected results with the instantly claimed SEQ ID NO:s, the instantly claimed genus-specific probes are considered to be functionally equivalent to those of Zhu because they are located within the same region, namely the 18S rRNA as the instantly claimed oligonucleotides and those of Zhu and further because Zhu teaches the usefulness of the 18S region for detecting Cryptosporidium.

With respect to conditions are provided, however the claims are drawn to a product which would hybridize necessarily under these conditions because there is 100% complementary.

The specific probes are considered to be functionally equivalent to those of Zhu because they are located within the same region, namely the 18S rRNA as the instantly claimed oligonucleotides and those of Zhu and further because Zhu teaches the usefulness of the 18S region for detecting and distinguishing between *C. parvum, C. muris, C. baileyi* and *C. wrairi.* The art also teaches that one of skill in the ad can modify the disclosed genus specific primer to enhance the properties based on factors such as probe length, melting temperature, and sequence content. Additionally, at the time the invention was made, the sequence of the Cryptosporidium nucleic acids of

distinct types were known and it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and within the skill of the art to obtain the instantly claimed oligonucleotides following the teachings of Hogan as to the identification of sequences that are genus specific and thus useful for the identification of Cryptosporidium by hybridization. Further, the teachings of Zhu, Williams, Xiao and Hogan indicate that the state of the art at the time the invention was made would have led one of ordinary skill in the art to the claimed genus-specific probes because Zhu, Williams, Xiao and Hogan teaches the usefulness of the 18S region of the Cryptosporidium for species-specific probes, species-specific primers and further teaches methods in which the probes may be modified.

Response to Arguments

The claims have been amended to require SEQ ID NO: 46 and 59 which are shown to significantly outperform a primer pair having SEQ ID NO: 45 and 59. When reviewing the specification, the specification appears to demonstrate the secondary considerations for primers CONSISTING of SEQ ID NO: 46 and 59. The secondary considerations are not taught for larger, smaller or hybridizable sequences. As provided by MPEP 716.02 "Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e)."

Conclusion

8. Claims 178-179, 219-224, 260-264 are objected to as being dependant on a rejected claim.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Rochelle et al. (Applied and Environmental Microbiology, Vol. 63, No. 1, pages 106-114, January 1997) teaches a method of using primers to the 18S to distinguish between *Crptosporidium parvum* and *Giardia lamblia* in water.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg
Primary Examiner
October 28, 2005